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RESEARCH ARTICLE

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The Effect of resistance training and growth hormone injection on circulating IGF-1 and IGFBP-3 levels in a rat model

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ABSTRACT

Growth hormone has mitotic and anti-apoptotic effects which may increase proliferation and transformation of cells when it is expressed aberrantly. This study investigated the effects of resistance training and growth hormone injection on circulating IGF-1, IGFBP-3 levels and IGF-1/IGFBP-3 ratio in male Wistar rats. Thirty-two male Wistar rats were randomly assigned to a control group (C, n = 8), a resistance training group (RT, n = 8), a growth hormone injection group (GI, n = 8) and a resistance training + growth hormone injection group (RG, n = 8). The resistance training protocol comprised of climbing a ladder (5 days/week, 3 sets/5 reps) while carrying a weight suspended from the tail. The growth hormone (2 mg/kg/day, 5 days/week) was injected before an exercise session. Serum IGF-1, IGFBP-3 levels, and IGF-1/IGFBP-3 ratio were measured after 8 weeks. One-way ANOVA analysis was used for comparison of serum IGF-1 and IGFBP-3 levels between groups. Serum IGF-1 levels and IGF-1/IGFBP-3 ratio significantly decreased, but serum IGFBP-3 levels showed no significant change in the RT group compared to the C group. Also, both serum IGF-1 and IGFBP-3 levels and IGF-1/IGFBP-3 ratio in GI and RG groups significantly increased compared to the other groups. In conclusion, resistance training decreases serum IGF-1 levels and/or IGF-1/IGFBP-3 ratio in normal condition. On the other hand, the growth hormone injection with and without the resistance training increases serum IGF-1 levels and IGF-1/IGFBP-3 ratio which could be noted as a condition with a higher risk of neoplasm.

Keywords

Resistance training; Growth hormone injection, IGF-1, IGFBP-3, Cancer

Abbreviations

GH: growth hormone
IGF-I: insulin-like growth factor type 1
IGF-1R: Insulin-like growth factor 1 receptor
IGFBPs: insulin-like growth factor binding proteins;
IGFBP-1-10: insulin-like growth factor binding protein 1-10
GTPase: guanosine triphosphatase
MAPK: mitogen-activated protein kinases
ERK: extracellular signal-regulated kinases
PI3K: phosphoinositide 3-kinase
AKT (PKB): Protein kinase B
mTOR: mammalian target of rapamycin;

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Introduction

Doping is a common phenomenon in the sports which has become more popular among different groups of people from adolescent and youth to non-elite and elite athletes, as well as non-sporting contexts by individuals who try to improve their appearance (1). Growth hormone (GH) is one of the doping agents that is used considerably for its anabolic and lipolytic properties (1, 2). GH stimulates the liver to produce insulin-like growth factors (IGFs), six common IGF binding proteins (IGFBP1-6) as well as other binding proteins (IGFBP7-10) which are discovered more recently (3). One of the main growth factors is IGF-1, which is an endocrine and auto/paracrine peptide expressed in the majority of cell types (4). GH affects the tissues by IGF-1 which stimulates mitosis and inhibits apoptosis. IGF-1 binds to its tyrosine kinase cell-surface receptor (IGF-1R) and activates [at least] two main signal-transduction pathways: 1) GTPase Ras-Raf-ERK/MAPK pathway and 2) PI3K/AKT pathway. Activation of these pathways stimulates proliferation and inhibits apoptosis which may lead in some conditions to malignant neoplasm (5).

Six types of IGFBPs have been known. IGFBPs act as important agents by attaching to IGFs and protect tissues from their undesirable effects. IGFBP-3 is the most abundant (more than 90%) IGF binding protein in circulation that modulates IGF-1 actions by enhancing and inhibiting IGF-1 bioavailability (6). Also, IGF-1 has an important role in the transformation and proliferation of cancer cells (7-10). In most cases, the elevated IGF-I concentrations are considered beneficial; however, cancer remains a significant exception. Some studies have shown that the increment of circulating IGF-1 levels or IGF-1/IGFBP-3 ratio and decrement of circulating IGFBP-3 levels are associated with higher risks of cancer. High levels of IGF-1significantly increase the risks of colorectal (11), breast (9), and prostate cancers (7, 8). At the same time, researchers determined that IGFBP-3 which binds to IGF-1 seems to neutralize it and reduce the risk of these malignancies (11). Circulating IGF-1 is positively associated with breast cancer risk and this association is not substantially modified by IGFBP-3 (9). In recent studies, high and normal plasma of IGF-1 and low levels of IGFBP-3 were independently associated with a greater risks of prostate cancer (7, 8, 12), premenopausal breast cancer (10, 13), lung cancer (14), bladder cancer (15) and colorectal cancer (16, 17). Therefore, optimizing the levels of IGF-1 and IGFBP-3 might decrease the risk of several cancers.

Physical activity is another potential mediator which influences the GH-IGF-1 axis. The increases, decreases, and no changes in circulating IGF-I and IGFBP-3 levels after both acute and chronic exercises have been reported (18-24), and such equivocal findings prevent definitive conclusions. Moreover, the effects of GH injection with resistance training on circulating IGF-1 and IGFBP-3 levels have not been studied.

Thus, the aim of this study was to examine the effects of 8-week GH administration with and without resistance training on circulating IGF-1 and IGFBP-3 levels in Wistar male rats.

Results

Compared to the control group, serum IGF-1 concentration significantly decreased in RT group (p = 0.048), while it significantly increased in GI (p = 0.001) and RG (p = 0.001) groups (Figure 1). Furthermore, serum IGFBP-3 concentration did not show any significant changes in RT group (p = 0.93). In contrast, serum IGFBP-3 concentration significantly increased in GI (p = 0.003) and RG (p = 0.011) groups, compared to the control group (Figure 2). In addition, the IGF-1/IGFBP-3 ratio was significantly lower in the RT group (p = 0.001). On the contrary, the ratio of IGF-1/IGFBP-3 was higher in both GI (p = 0.001) and RG (p = 0.001) groups compared to other groups (Figure 3).

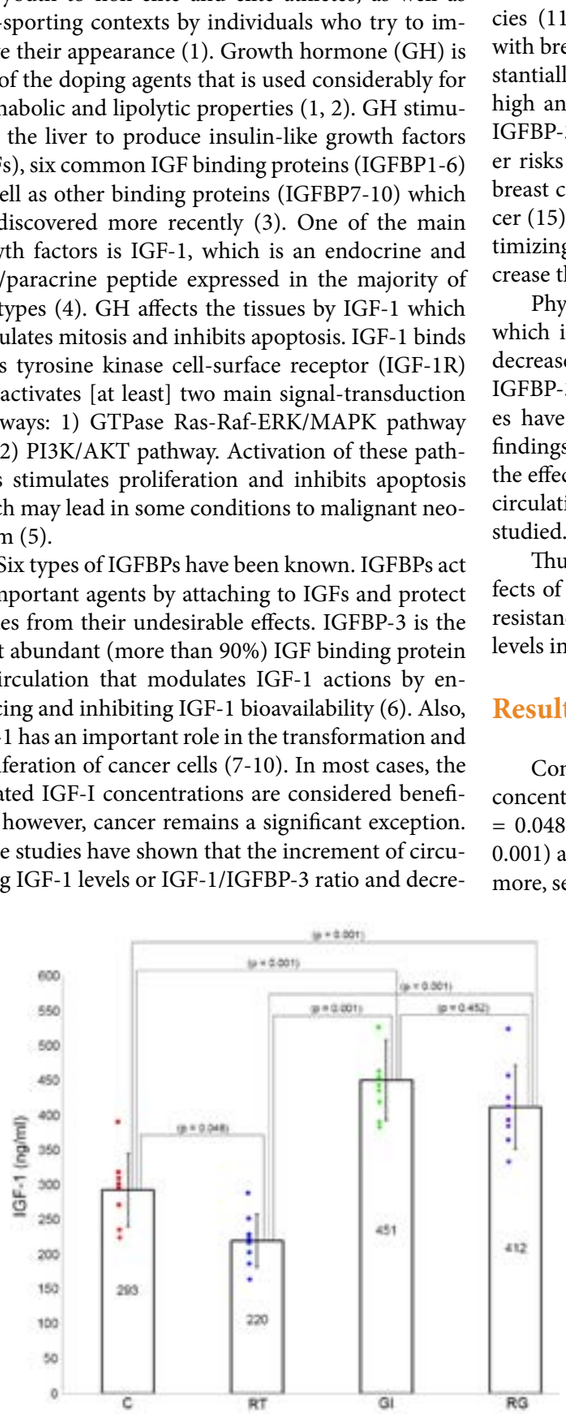

Figure 1
Comparison of circulating IGF-1 levels between control (C) resistance training (RT), growth hormone-injected (GI) and Resistance training + growth hormone-injected (RG) groups. Values are expressed as mean (± SD). Significant differences between groups are shown as $p < 0.05$.

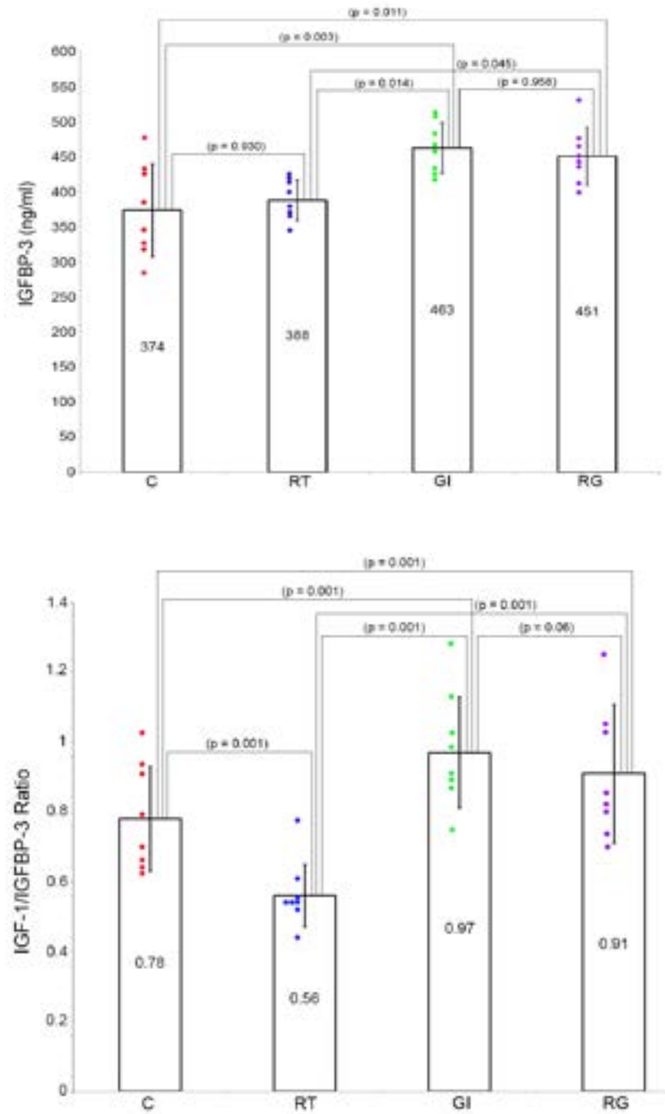

Figure 2
Comparison of circulating IGFBP-3 levels between control (C) resistance training (RT), growth hormone-injected (GI) and resistance training + growth hormone-injected (RG) groups. Values are expressed as mean (± SD). Significant differences between groups are shown as $p < 0.05$.

Figure 3
Comparison of circulating IGF-1/IGFBP-3 ratio between control (C) resistance training (RT), growth hormone-injected (GI) and resistance training + growth hormone-injected (RG) groups. Values are expressed as mean (± SD). Significant differences between groups are shown as $p < 0.05$.

Discussion

We have examined the response of circulating IGF-1 and IGFBP-3 levels to GH injection with resistance training. The results of our study showed that resistance training reduced serum IGF-1 concentration. Some studies have already reported that acute resistance and endurance exercise increase serum IGF-1 concentration temporarily, which typically returns to baseline after 10 to 15 minutes (20, 23, 25, 26). However, other studies have demonstrated that chronic exercise training causes an increase (18, 21, 27), no change (28, 29), or a decrease (24, 30, 31) in circulating level

of IGF-1, which is equivocal. Nindl et al. stated that although local IGF-1 is up-regulated with both acute and chronic exercises, circulating IGF-1 may actually decrease (32). The decrement of circulating IGF-1 in this study might be due to the anabolic role of IGF-1. Decreased circulating levels of IGF-1in response to short-term chronic training (>12 wk), might be related to neuromuscular anabolic adaptations (32). It has been suggested that physical activity might increase the uptake of IGF-1 into peripheral tissues (33) and central nervous system (34). On the other hand, GH injection caused an increment in IGF-1 with and without resistant training. Recently, a positive correlation between the level of IGF-1 and the risks of several cancers such as colorectal, breast, prostate, lung cancer was found (35). According to cell proliferation and apoptosis inhibitor roles of IGF-1, previous studies have indicated that increased circulating IGF-1 level, decreased circulating IGFBP-3 and/or increased IGF-1/IGFBP-3 ratio might be involved in the commencement of these cancers (5). The consequence of binding IGF-1 to its receptor (IGF-1R) is the phosphorylation of insulin receptor substrate -1 (IRS-1). Subsequently, phosphoinositide 3-kinase (PI3K) is activated and increases phosphatidylinositol 3,4,5-triphosphate (PIP3), which activates the critical protein AKT/PKB through phosphorylation. As a result, the AKT protein stimulates the release of anti-apoptotic protein Bcl-2 from bad and activates protein synthesis through mTOR. All these actions are related to PI3K/AKT pathway of IGF-1 signaling which is ultimately responsible for cell death prevention (5).

Simultaneously, IGF-1 signaling increases cell proliferation through the Ras/MAPK pathway. After IGF-1 binding to IGF-1R and activating IRS protein SHC, GTPase Ras can stimulate Raf. Raf activates a kinase cascade which leads to the activation of mitogen-activated protein kinases (MAPKs), ERK1 and ERK2. Afterward, these MAPKs phosphorylate and activate multiple targets, in particular, the transcription factor ELK1 which increases gene expression and leads to cell growth (5). The imbalance between these pathways may result in the creation of neoplasm.

Secondly, we have found that circulating IGFBP-3 did not show any significant changes after resistance training. In spite of this, GH injection increased circulating IGFBP-3 levels with and without resistance training. IGFBPs are crucial regulators of IGF-1 actions and alter plasma levels of free IGF-I without affecting total IGF-I (4). It has been shown that resistance exercise changes the concentrations of IGFBPs which affects the biological activity of IGF-1 (21). IGFBP-3 is the most abundant protein that carries IGF-1, and lowers the free concentration of IGF-I and protects IGF-I from degradation (36). The results of previous studies are also inconsistent with the effects of exercise training on circulating IGFBP-3 levels (23, 26, 27, 37). Nishida et al. showed that after 6 weeks of aerobic training, circulating IGF-1 levels decreased by 9% and IGFBP-3 did not change significantly (30). Nindl et al. observed a significant increase of IGFBP-3 after resistance exercise and a decrease to the baseline during the next 13 hours (38). Chicharro et al. discussed that 3 weeks of endurance competition did not change circulating IGFBP-3 levels, but it decreased IGF-1 levels (31). These glaring inconsistencies between studies might be due to the type of exercise, training volume, duration of the intervention and age, training background and nutritional status of participants (29, 32).

Finally, in the present study, resistance training decreased IGF-1/IGFBP-3 ratio, whereas GH injection with and without resistance training increased IGF-1/IGFBP-3 ratio. It has been stated that the IGF-1/IGFBP-3 ratio is a biomarker for bioavailability of circulating IGF-1 levels (39). Thus, decreased or increased IGF-1/IGFBP-3 ratio might be related to a lower and higher risk of cancer, respectively.

The results of the present study led us to conclude that resistance training decreases circulating IGF-1 levels and/or IGF-1/IGFBP-3 ratio in normal condition. On the contrary, GH injection with and without resistance training increases circulating IGF-1 levels and/or IGF-1/IGFBP-3 ratio which could be considered as a condition with a higher risk of neoplasm. Further studies are required to extend these results in order to discover the exact resistance training effects on IGF-1 and IGFBP-3 concentration, and to examine the risk of cancer types after GH injection which increases the circulating IGF-1 levels and/or IGF-1/IGFBP-3 ratio.

Material and methods

Animals

Thirty-two Wistar male rats, 12 weeks of age, were purchased from Razi Vaccine and Serum Research Institute of Mashhad. All rats were randomly divided into four groups. Each day, all the animals were injected subcutaneously with either GH or saline (5 times per week for 8 weeks). GH was injected 1 h prior to the exercise. Group C was injected with saline using the same method used for the GH injection groups. Group RT was injected with saline and subjected to resistance training. Group GI was injected with human recombinant growth hormone (Genotropin, Germany) with a dose of 2 mg/kg (BW) 5 days per week. Group RG was injected with human recombinant growth hormone and also subjected to resistance training. All rats were weighed weekly, and the hormone dose was adjusted according to body weight. All rats were housed under controlled conditions and had unlimited access to water and food pellets. The animals' room temperature was maintained at 22 ± 1°C with a 12 h light/dark cycle. Experimental protocols were approved by the Institutional Animal Ethics Committee of Ferdowsi University of Mashhad (Ethic code: IR.MUM.FUM.REC.1396.12).

Resistance training

After the first week of adaptation, training protocol started, rats were trained 5 days a week for the next 8 weeks. Resistance training was accomplished by using a 1 m high ladder with 2 cm grid steps and an 85° grade. In their first week, rats were familiarized with climbing up to the top cage with and without weight on their tails. The weight, in an acryl tube, was attached to the tail with a plastic belt and tapes. Rats started their climbing from the bottom of the ladder and they were forced to climb up to the top by touching and shouting. Training sessions were started with the intensity at 50% of each rat's bodyweight and increased (10% per week) gradually throughout the eight weeks of the training period. The resistance training consisted of three sets of five repetitions with a one-minute rest interval between the repeats and two minutes between the sets. This procedure was repeated until either the rat finished all three sets of training or failed to climb the entire length of the ladder (40).

Measurement of IGF-1 and IGFBP-3

Food was withheld for 12 h, and GH or exercise was withdrawn 72 h before the rats were anesthetized with 75 mg/Kg ketamine and 25 mg/Kg xylazine and killed. The serum was collected by centrifugation at 3000 RPM for 15 min at 4 °C and then stored at −20 °C until the analysis commenced. Serum IGF-1 and IGFBP-3 levels were measured by ELISA kits (Hangzhou East biopharma, Elisa Kits, CAT.NO: CK-E30653- E91558) according to the manufacturer's protocol with a lower limit of detection of 1.55 ng/ml and 0.93 ng/ml, respectively.

Statistical analysis

The Shapiro-Wilk test was applied to display the normality of data distribution. The mean of circulating IGF-1 and IGFBP-3 levels and IGF-1/IGFBP-3 ratio were compared by One-way ANOVA analysis. The Tukey's test was used post hoc to identify significant differences between groups. $p < 0.05$ was taken to denote statistical significance. Data were analyzed using SPSS software (version 20, SPSS Inc). All data are reported as mean (± SD). Significant differences between groups are shown as $p < 0.05$.

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Author Contributions

BR performed the design and coordinated the study, participated in all of the experiments and wrote the manuscript with support from MM, AR and ZM. MM and AR conceived the idea of research and helped supervise all the stages of the project. AJ contributed to the analysis of the results and to the writing of the manuscript.

Conflict of Interest

We have no conflicts of interest to disclose.

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